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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,316	08/27/2001	Christopher Reeves	300622002611	5488

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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	10

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

.Offic Action Summary	Application N .	Applicant(s)	
	09/940,316	REEVES ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

1. Claims 1-20 are pending in the instant application. Said claims are drawn to more than one invention and are subject to restriction.

Improper Markush Groups

2. Claim 1 contains an improper Markush groups. In a proper Markush group, "the subject matter in the claim lacks unity of invention"; "broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility" (see M.P.E.P. § 803.02). In Claim 1, the common utility disclosed for the Markush members is that the nucleic acids encode products which synthesize FK-520; however, the various fragments of nucleic acids (encoding a CoA ligase, a non-ribosomal peptide synthase, **OR** a domain of an extender module of a PKS enzyme) do not share a common structural feature. Moreover, if "the members of the Markush groups are sufficiently few on number or so closely related that a search and examination of the entire claim can be made without serious search burden, the examiner must examiner all claims on the merits" (see M.P.E.P. § The specification is objected to for being confusing with respect to the sequence listing. The sequence listing contains 155 sequences. Every SEQ ID NO is mentioned in the specification and/or the claims except SEQ ID NOs: 76-83. It is unclear why said sequences are in the sequence listing if they are not described in the specification. All SEQ ID NOs in the sequence listing must be described in the specification. Appropriate correction is required.803.02); thus, the Examiner would examine the entire

Markush group of the various claims is such examination did not present a serious search burden - that is not the case here.

Because the Markush group in Claim 1 is improper, the single claim can be grouped separately with its members as distinct inventions in the restriction requirement below.

3. Claim 7 contains an improper Markush group. The above section describes a proper Markush group. Absent evidence to the contrary, any one of the 4 cosmids claimed present nucleic acids with different structural features with respect to the other plasmids. However, if applicants can identify significant portions of overlap among the cosmids, the Markush group may be reconsidered. Notwithstanding additional evidence concerning their common structural features, a search of more than one of these large cosmids with the elected group in a single application would present a serious search burden on the Office.

4. Claims 12-16 contain improper Markush groups. The above section describes a proper Markush group. Claims 12-16 relate to host cells expressing two modified, distinct PKSs, either modified FK-520 PKS **OR** modified FK-506 PKS. Host cells expressing modified FK-520 PKSs have different structural features than host cells expressing modified FK-506 PKSs.

Because the Markush group in Claims 12-16 is improper, this set of claims can be grouped separately with its members as distinct inventions in the restriction requirement below.

Restriction

5. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claim 1-8, drawn to isolated nucleic acids encoding an open reading frame of a gene cluster that produces FK-520 comprising a CoA ligase domain (fkbB), classified in class 536, subclass 23.2.

II. Claim 1-8, drawn to isolated nucleic acids encoding a non-ribosomal peptide synthetase (fkbP), classified in class 536, subclass 23.2.

III. Claim 1-8, drawn to isolated nucleic acids encoding an open reading frame of a gene cluster that produces FK-520 (fkbC), classified in class 536, subclass 23.2.

IV. Claim 1-8, drawn to isolated nucleic acids encoding an open reading frame of a gene cluster that produces FK-520 (fkbA), classified in class 536, subclass 23.2.

V. Claims 9-11, drawn to methods of preparing polyketides using nucleic acids encoding an open reading frame of a gene cluster that produces FK-520 comprising a CoA ligase domain (fkbB), classified in class 435, subclass 76.

VI. Claims 9-11, drawn to methods of preparing polyketides using nucleic acids encoding a non-ribosomal peptide synthetase (fkbP), classified in class 435, subclass 76.

VII. Claims 9-11, drawn to methods of preparing polyketides using nucleic acids encoding an open reading frame of a gene cluster that produces FK-520 (fkbC), classified in class 435, subclass 76.

VIII. Claims 9-11, drawn to methods of preparing polyketides using nucleic acids encoding an open reading frame of a gene cluster that produces FK-520 (fkbA), classified in class 435, subclass 76.

IX. Claims 12-16, drawn to host cells expressing PKSs of FK-520, classified in class 435, subclass 252.35.

X. Claims 12-16, drawn to host cells expressing PKSs of FK-506, classified in class 435, subclass 252.35

XI. Claim 17, drawn to host cells comprising recombinant genes encoding enzymes to synthesize ethylmalonyl CoA or 2-hydroxymalonyl CoA, classified in class 435, subclass 252.35.

XII. Claims 18-20, drawn to polyketides, classified in class 568, subclass 382.

6. The inventions are distinct, each from the other, because of the following reasons:

Groups I-IV are related as nucleic acids encoding enzymes which can be a member of a polyketide synthase enzyme cluster. However, these enzymes (i.e. CoA ligases, non-ribosomal peptide synthetase, and domains of an extender module of an FK-520 polyketide synthase

enzyme) each have distinct functional properties catalyzing unique reactions in the biosynthetic pathway of the polyketide FK-520. Furthermore, these enzymes have distinct structural properties with varying amino acid sequence lacking any consensus among the groups. Moreover, each of these enzymes can be used in a distinct process from the biosynthesis of the polyketide FK-520. Thus, Groups I-IV are patentably distinct, each from the other.

Groups I-IV are respectively related to Groups V-VIII as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the nucleic acids of Groups I-IV can be used to produce other materially different products than the polyketides produced in the methods of Groups V-VIII; for example, the nucleic acids of Groups I-IV can be used in hybridization assays to identify other PKS-encoding nucleic acids in other polyketide-producing bacteria. Thus, Group I is patentably distinct from Group V, Group II is patentably distinct from Group VI, Group III is patentably distinct from Group VII, and Group IV is patentably distinct from Group VIII.

Group I is unrelated to Groups VI-VIII, Group II is unrelated to Groups V and VII-VIII, Group III is unrelated to Groups V-VI and VIII, and Group IV is unrelated to Groups V-VII. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (M.P.E.P. § 806.04, M.P.E.P. § 808.01). In the instant case, the methods are not required to use the products of unrelated product Group in the method as a reagent. Thus, Group I is patentably distinct from

Groups VI-VIII, Group II is patentably distinct from Groups V and VII-VIII, Group III is patentably distinct from Groups V-VI and VIII, and Group IV is patentably distinct from Groups V-VII.

Groups I-IV are related to Group IX as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (M.P.E.P. § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of each of the subcombinations as claimed because the combination is drawn to host cells having *modified* nucleic acids encoding FK-520 PKS; when such a modification is in the nucleic acid of the subcombination, the combination no longer contains the subcombination. The subcombinations have separate utility such as recombination with nucleic acids encoding other PKSs, such as rapamycin-encoding nucleic acids. Thus, Groups I-IV are each patentably distinct from Group IX.

Groups I-IV are related to Group X as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (M.P.E.P. § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of each of the subcombinations as claimed because the combination is drawn to host cells having modified nucleic acids encoding FK-506 PKS; while the modification *can* include an FK-520-encoding nucleic acid, such a modification is not required to produce the combination. The

subcombinations have separate utility such as recombination with nucleic acids encoding other PKSs, such as rapamycin-encoding nucleic acids. Thus, Groups I-IV are each patentably distinct from Group X.

Groups I-IV are related to Group XI as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (M.P.E.P. § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of each of the subcombinations as claimed because the combination is drawn to host cells having recombinant genes encoding enzymes which synthesize ethylmalonyl CoA or 2-hydroxymalonyl CoA; many PKS genes and other genes can fit this criteria so that the combination no longer contains the subcombination. The subcombinations have separate utility such as recombination with nucleic acids encoding other PKSs, such as rapamycin-encoding nucleic acids. Thus, Groups I-IV are each patentably distinct from Group XI.

Groups I-IV are unrelated to Group XII. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (M.P.E.P. § 806.04, M.P.E.P. § 808.01). In the instant case, the nucleic acids of Groups I-IV are wholly different products having distinct structures and functions from the polyketides of Group XII. Thus, Groups I-IV are each patentably distinct from Group XII.

Groups V-VIII are related as methods which all utilize nucleic acids encoding CoA ligases, non-ribosomal peptide synthetase, or domains of extender modules of an FK-520

polyketide synthase enzyme. However, these method steps have distinctly different reagents which can produce distinctly different products. Thus, Groups V-VIII are patentably distinct, each from the other.

Groups V-VIII are unrelated to Groups IX-X. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (M.P.E.P. § 806.04, M.P.E.P. § 808.01). In the instant case, the methods of Groups V-VIII use host cells having nucleic acids encoding wild-type FK-520 PKS. However, the methods of Group IX use nucleic acids encoding modified FK-520 PKSs; and the methods of Group X use nucleic acids encoding a wholly different PKS, FK-506 encoding PKS. Thus, each of Groups V-VIII are patentably distinct from each of Groups IX-X.

Groups V-VIII are unrelated to Group XI. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (M.P.E.P. § 806.04, M.P.E.P. § 808.01). In the instant case, the methods of Groups V-VIII use host cells having nucleic acids encoding wild-type FK-520 PKS while the methods of Group XI only require nucleic acids encoding a enzyme which can synthesize ethylmalonyl CoA or 2-hydroxymalonyl CoA. Thus, Groups V-VIII are patentably distinct from Group XI.

Groups V-VIII and Group XII are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the

instant case, the polyketides can be made by another and materially different process such as organic synthesis. Thus, Groups V-VIII are patentably distinct from Group XII.

Groups IX-X are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (M.P.E.P. § 806.04, M.P.E.P. § 808.01). In the instant case, host cells having either modified FK-520 encoded enzymes, modified FK-506 encoded enzymes, or ethylmalonyl or 2-hydroxymalonyl encoded enzymes are not disclosed as being used together and produce different polyketide products. Thus, Groups IX-X are patentably distinct, each from the other.

Groups IX-X are unrelated to Groups XI and XII. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (M.P.E.P. § 806.04, M.P.E.P. § 808.01). In the instant case, the host cells of Groups IX-X are wholly different products having distinct structures and functions from the host cells of Group XI and the polyketides of Group XII. Thus, Groups IX-X are each patentably distinct from Groups XI-XII.

Notice of Possible Rejoinder

7. The Examiner notes that if claim 6 is elected and found directed to an allowable product, then claims 9-11, which are directed to the process of using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, would now be rejoined pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also MPEP 821.04, *In re Ochiai,* and *In re Brouwer*). Since process claims 9-11 would be rejoined and fully examined for patentability under 37 C.F.R. § 1.104, applicants are

instructed to amend said claims as deemed necessary according to rejections made against the elected claims.

Election

8. A telephone call was made to Carolyn Favorito on June 9, 2003 to request an oral election to the above restriction requirement but did not result in an election being made.

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(i).

Conclusion

9. A complete reply to this requirement MUST include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. § 1.143).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
June 9, 2003